Emotional orienting during interoceptive threat in orthostatic intolerance: dysautonomic contributions to psychological symptomatology in the postural tachycardia syndrome and vasovagal syncope

Article (Accepted Version)

Emotional orienting during interoceptive threat in orthostatic intolerance: Dysautonomic contributions to psychological symptomatology in the postural tachycardia syndrome and vasovagal syncope

Andrew P Owens[1,2,3*], David A Low[4], Hugo D Critchley[5,6,7], Christopher J Mathias[2,8]

1. Lab of Action and Body, Department of Psychology, Royal Holloway, University of London, UK
2. Department of Brain Repair and Rehabilitation, Institute of Neurology, University College London, UK
3. Autonomic Unit, National Hospital Neurology and Neurosurgery, UCL NHS Trust, London, UK
4. School of Sport and Exercise Sciences, Liverpool John Moores University. Liverpool, UK.
5. Neuroscience, Brighton and Sussex Medical School, Brighton, UK
6. Sussex Partnership NHS Foundation Trust, Brighton, UK
7. Sackler Centre for Consciousness Science, University of Sussex, UK
8. Autonomic & Neurovascular Medicine Centre, Hospital of St John & St Elizabeth, London, UK

Corresponding author: Dr Andrew Owens

Corresponding author's address: Lab of Action & Body, Department of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EXU

Corresponding author's phone and fax: +44 (0)1784 276551

Corresponding author's e-mail address: andrew.owens@rhul.ac.uk

Number of words in abstract: 216

Number of words in main text: 3142

Number of figures: 2

Number of tables: 3

Keywords: autonomic nervous system, dysautonomia, interoception, orienting response, orthostatic intolerance, postural tachycardia syndrome, vasovagal syncope

Abstract

Cognitive and emotional processes are influenced by interoception (homeostatic somatic feedback), particularly when physiological arousal is unexpected and discrepancies between predicted and experienced interoceptive signals may engender anxiety. Due to the vulnerability for comorbid psychological symptoms in forms of orthostatic intolerance (OI), this study investigated psychophysiological contributions to emotional symptomatology in 20 healthy control participants (13 females, mean age 36 ± 8 years), 20 postural tachycardia syndrome (PoTS) patients (18 females, mean age 38 ± 13 years) and 20 vasovagal syncope (VVS) patients (15 females, mean age 39 ± 12 years). We investigated indices of emotional orienting responses (OR) to randomly presented neutral, pleasant and unpleasant images in the supine position and during the induced interoceptive threat of symptom provocation of head-up tilt (HUT). PoTS and VVS patients produced greater indices of emotional responsivity to unpleasant images and, to a lesser degree, pleasant images, during interoceptive threat. Our findings are consistent with biased deployment of response-focused emotion regulation (ER) while patients are symptomatic, providing a mechanistic underpinning of how pathological autonomic overexcitation predisposes to anxiogenic traits in PoTS and VVS patients. This hypothesis may improve our understanding of why orthostasis exacerbates cognitive symptoms despite apparently normal cerebral autoregulation, and offer novel therapeutic targets for behavioural interventions aimed at reducing comorbid cognitive-affective symptoms in PoTS and VVS.

1 Introduction

Cognitive and emotional processes are influenced by interoception (homeostatic somatic feedback) (1-3), particularly when physiological arousal is abnormal and discrepancies between predicted and experienced interoceptive signals may engender anxiety (4, 5) (6). Baroreceptor pathways directly relay cardiovascular interoceptive information to brainstem centres, where normative baroreflex function is subject to modulation by 'top-down' brain activity by descending forebrain (e.g. prefrontal cortex) and hypothalamic signalling on medullary centres, including the nucleus of the solitary tract (7). Dysfunction of the baroreflex causes orthostatic intolerance (OI) and syncope due to cerebral hypoperfusion. Two common clinical forms of OI are the postural tachycardia syndrome (PoTS) (prevalence of >170 cases per 100,000 in the general population (8)) and vasovagal syncope (VVS) (accounting for 40% of faints (9)).

PoTS is defined by an excessive orthostatic HR increase, of >30 beats per minute (BPM) or a HR of >120 BPM, without orthostatic hypotension (fall of > 20 mmHg systolic BP (SBP) or >10mmHg diastolic BP (DBP) (10) within 10 mins of orthostasis or head-up tilt (HUT). Symptoms include dizziness and palpitations when upright; some have orthostatic headache, fatigue, bladder and gastrointestinal (GI) symptoms (11). Take out functional impairment as not a symptom (12). Infection (13), deconditioning (14) and hypovolemia have also been implicated in PoTS pathophysiology and can worsen symptoms. Some divide PoTS into hyperadrenergic or neuropathic phenotypes (15).

The lifetime incidence of syncope is approximately 39% (18,19) and accounts for 3-5% of emergency room admissions (20-22). There are various conditions that cause syncope, including cardiac causes. Neurally mediated syncope (NMS) are probably the most prevalent, as reported in certain age groups, such as teenagers and the young. It comprises situation, vasovagal (VVS) and carotid sinus hypersensitivity. Of the different causes of NMS the most common is VVS, which is characterised by a paroxysmal malfunction of baroreflex function and autonomic instability during which aberrant sympathoexcitation (e.g. palpitations, sudomotor activation) often precedes sympathetic withdrawal causing profound vasodilatation, a fall in BP, as well as vagal/parasympathetic excitation with a fall in HR and cardiac output, resulting in syncope (16, 17). In many patients, perceived physical and psychosocial stressors may also induce VVS (18).

Consistent with the perturbed integration of central and autonomic nervous system (ANS) function (19, 20), psychological symptoms are overrepresented in PoTS and VVS (21). In PoTS, the profile of cognitive-affective symptoms includes anxiety, attentional deficits, impaired working memory, somatic hypervigilance and subjective 'brain-fog' (22) (23-25) (26). Cognitive symptoms are typically exacerbated by orthostasis and autonomic symptom provocation (27) but despite investigations into cerebral blood flow, sleep behaviour and neurotransmitter function, the cause of this brain-fog remains elusive in PoTS patients (28, 29). In VVS, depression, anxiety and blood-injection-injury phobia are common (30-33). Moreover, heightened anxiety levels increase the risk of VVS during HUT (34) and can determine frequency and severity of syncopal episodes (35). During induced emotional stress, VVS patients also evidence reduced anticipation and regulation of emotional states (36) and patients with psychiatric disorders, such as psychogenic fever, report symptoms similar to VVS and PoTS, such as light-headedness and fatigue (37).

In a recent study (38) by our group, we found most cognitive-affective symptoms in PoTS and VVS patients are typically subclinical, without strong causative links to personality (neurosis, trait anxiety) or traumatic experience. Instead, symptoms appeared better explained by 'interoceptive' anxiety of physical sensations and dysautonomic symptoms. This was further supported by observed deficits in interoceptive accuracy and anxiogenic interpretation of interoceptive signals by PoTS and VVS patients during head-up tilt (HUT).

The orienting response (OR) encompasses a series of involuntary sensory, motor, parasympathetic and sympathetic adjustments that occur in response to the presentation of a salient stimulus. When the stimulus is emotive, especially unpleasant, the OR is more robust (39). Evoked cardiac deceleration (ECR1) is the earliest component of the OR, and is centrally mediated by 'defence' circuitry, including the amygdala (40), and peripherally mediated by the vagus nerve. The OR facilitates perception of the stimulus, including inhibition of conditioned and unconditioned reflexes (41) to 'increase analyser sensitivity' (42). Despite autonomic orchestration of the visceral non-muscular components of the OR, there have been no investigations into whether dysautonomia effects ORs or related psychological processes, for example, if the OR inhibits conditioned and unconditioned reflexes, does this include dysautonomic symptom provocation? This is relevance to conditions such as PoTS and VVS in which autonomic overexcitation is expressed with a prevalence of comorbid psychological symptoms. If interoception is at the core of psychological symptomatology in PoTS and VVS, the generation of

emotional ORs may be exaggerated by orthostatic challenge, where the interoceptive threat of OI symptom provocation would amplify 'bottom-up' stress.

The current study extends description of the link between OI, interoception and psychological symptoms by examining emotional ORs in PoTS and VVS in comparison to healthy controls. We predicted interoceptive threat/symptom provocation would exacerbate low-order emotional responsivity during HUT in PoTS and VVS patients.

2 Materials and methods

2.1 Participants

All experimental procedures received national and institutional ethical approval (NRES Committee London - Harrow, University College London Healthcare Trust Research and Design Office, Imperial College London AHSC Joint Research Compliance Office). Twenty healthy control participants (13 females, mean age 36 $\pm$ 8 years), twenty PoTS patients (18 females, mean age 38 $\pm$ 13 years) and twenty VVS patients (15 females, mean age 39 $\pm$ 12 years) gave full informed consent to participate in the study. The predominance of females in this study's patients groups is due to PoTS being more common in women (female:male ratio, 4.5:1) (11, 15). Patients with any current psychiatric comorbidities requiring treatment were not included in the current study.

2.2 Supine and head-up tilt baseline protocol

Participants were instructed to withdraw any medication and/or abstain from any stimulants that may affect autonomic function on the day of testing, such as beta-adrenergic blockers, vasodilators, nicotine and caffeine. Normative heart rate (HR) and blood pressure (BP) data was collected from participants over 10 mins supine baseline and 10 mins HUT baseline periods using PowerLab 16/30, AD Instruments, Oxford, United Kingdom. BP was continually recorded using digital photoplethysmography (Finometer, FMS, NL).

2.3 Orienting response protocol

Originally believed to be a unitary reflex (42), Barry's development of the 'Preliminary Process Theory' redefined the OR (43). The early evoked cardiac response of HR deceleration (ECR1) of the OR indicates stimulus detection (43, 44), with the degree of cardiac deceleration predicting subsequent memory performance (45). ECR1 is differentiated from the cardiac defence response (CDR) by the defining cardiac acceleration during the CDR to an intense or aversive stimulus, which reduces attention and perception to protect against the stimulus (46). It is widely accepted that the OR is therefore the opposite of the CDR. The PVC component of the OR provides an index of stimulus strength, as it shows substantial linear effects of intensity with no decrement in response with stimulus repetition (43). This study therefore focused on both the ECR1 and PVC components of the OR as (i) neither have habituation effects, (ii) both provide indices of attentional and emotional mechanisms and (iii) are the most likely components of the OR to be compromised by autonomic cardiovascular pathophysiology in PoTS and VVS. PVC was extracted from the beat-to-beat measures of diastolic blood pressure from continuous digital photoplethysmography. In line with previous guidelines, ORs were analysed for 6 secs post-stimulus presentation and followed by an Inter Trial Interval (ITI) of 10 secs (47). The last 1 secs of the ITI prior to stimulus presentation acted as baseline and change scores for each 1 secs of the total 6 secs were calculated by subtracting the baseline from each 1 secs estimate.

ORs to randomly presented emotional images were recorded at supine rest and during HUT. Participants viewed a series of images presented 1 metre from their head and informed to keep their eyes fixed on the screen but remain non-responsive during stimulus presentation. Images were taken from the International Affective Picture System (IAPS) and presented in two sets. IAPS is a database of images covering a range of emotional valences (categorised into neutral, pleasant and unpleasant), dominance ratings and arousal scores. There is extensive normative data on the IAPS which has been widely used as a robust investigative tool in emotional paradigms in clinical and non-clinical cohorts (48, 49).

Image Set 1 consisted of 12 neutral images, 13 unpleasant images and 13 pleasant images (mean valence 5.07 $\pm$ 1.4, mean arousal 4.38 $\pm$ 2.2, dominance 1 mean 5.35 $\pm$ 2.1, dominance 2 mean 4.60 $\pm$ 2.1), presented in a randomised order. Set 2 consisted of 12 neutral images, 14 unpleasant images and 12 pleasant images (mean valence 5.07 $\pm$ 1.4, mean arousal 4.38 $\pm$ 2.2, dominance 1 mean 5.6 $\pm$ 2.1, dominance 2 mean 5.2 $\pm$ 2.1), presented in a randomised order. One image set was presented

whilst the participant was supine and the other image set during 60° HUT. In-between the supine and HUT phases of the protocol, there was a 5-10 mins wash-out period to allow autonomic data to return to basal levels. ORs were recorded and analysed identically for the supine and HUT protocols. HUT was terminated if syncope or presyncope occurred or if OI symptoms become too difficult for the participant to tolerate.

2.4 Statistical analysis

Statistical analysis was performed using SPSS (version 20). Descriptive statistics are presented as mean (± 1 SD) for normally distributed data. To test the prediction of increased ORs to emotive images in patients, during the induction of interoceptive threat by HUT, we tested for the appropriate interaction between group and condition when explaining OR. Specifically, we used an analysis of variance with three factors; (i) group with three levels (healthy control subjects; PoTS patients; VVS patients), (ii) condition with two levels (supine; HUT) and (iii) stimulus valence with three levels (neutral, pleasant and unpleasant). The effect we hypothesised corresponds to an elevated OR in clinical subjects to emotive stimuli during symptom provocation/interoceptive threat during HUT. Statistical significance was specified as a 2-tailed p-value of <0.05.

3 Results

3.1 Supine and head-up tilt baseline

One VVS patient experienced presyncope during baseline HUT and was withdrawn from the study. There were no group differences in supine baseline measures. PoTS patients' HR was significantly (p=.005) increased during baseline HUT in comparison to healthy controls due to the provocation of orthostatic tachycardia (Table 1).

	Supine HR (BPM)	Supine SBP (mmHg)	Supine DBP (mmHg)	Head-up tilt HR (BPM)	Head-up tilt SBP (mmHg)	Head-up tilt DBP (mmHg)
Controls	72 ± 11.9	127.7 ± 29.1	68.7 ± 20.5	79.5 ± 10.1	131.8 ± 21	75.3 ± 14.1
PoTS	73.3 ± 11.2	127.7 ± 15.3	67.3 ± 8.6	94.7 ± 14.1*	126 ± 28.6	67.1 ± 13.3
VVS	71.1 ± 12.1	136.3 ± 43.8	60.9 ± 22.4	71.5 ± 12.7	138.3 ± 42	61.8 ± 21.7

Table 1. Supine baseline and head-up tilt autonomic indices in healthy controls, postural tachycardia syndrome patients and vasovagal syncope patients. HR = heart rate, BPM = beat per minute, SBP = systolic blood pressure, DBP = diastolic blood pressure, ± = standard deviation, * = statistically significant (p<.05)

3.2 Orienting responses

3.2.1 Emotionally neutral stimuli

One PoTS patient became too tachycardic to continue testing during simultaneous emotional stimulus presentation and HUT. During simultaneous randomly presented emotional stimuli on HUT, PoTS patients HR was significantly higher than control and VVS subjects due to the provocation of orthostatic tachycardia. There were no between-group differences in OR-related ECR1 and PVC during supine or HUT neutral image presentation.

3.2.2 Emotionally pleasant stimuli

There was a significant effect of interoceptive threat on ORs to pleasant images. There were no between-group differences in OR-related ECR1 and PVC during supine pleasant image presentation. During HUT pleasant image presentation, there were significant between-group differences in PVC at 3 secs (F(2, 42)=4.86, p=.013), 4 secs (F(2, 42)=3.98, p=.026), 5 secs (F(2, 42)=3.79, p=.031) and 6 secs (F(2, 42)=3.63, p=.035) (figure 1). There were no significant between-group differences amongst PoTS and VVS patients (table 2).

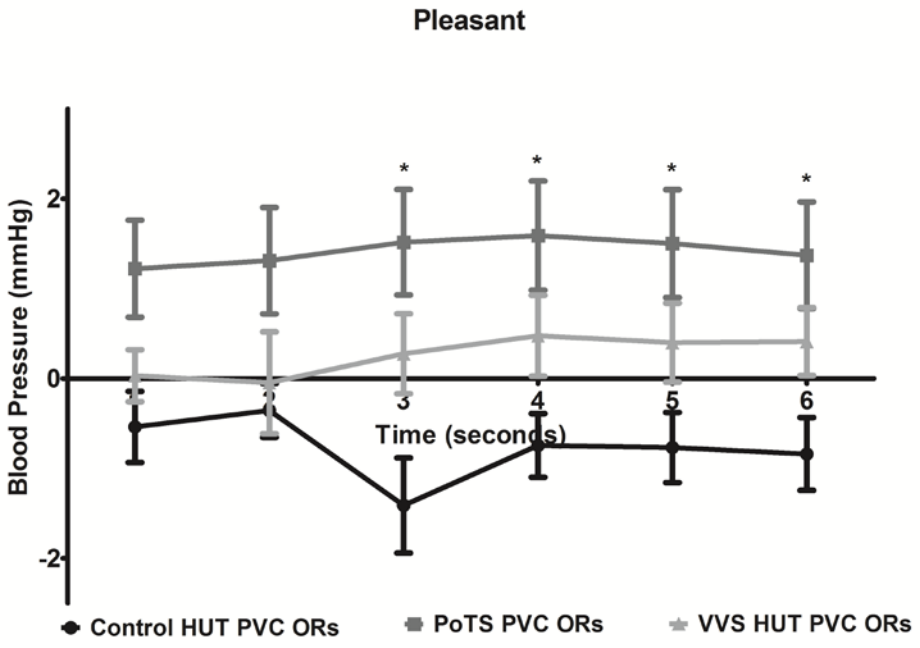

Figure 1. Stimulus intensity peripheral vasocontraction (PVC) orienting responses (ORs) to randomly presented pleasant images during head-up tilt (HUT). PoTS = postural tachycardia syndrome, VVS = vasovagal syncope. Error bars = ± standard deviation, * = statistically significant (p<.05)

	Controls	PoTS	VVS
HUT PVC 1 secs	-0.38 mmHg ± 1.86	1.22 mmHg ± 2.41	0.03 mmHg ± 1.29
HUT PVC 2 secs	-0.15 mmHg ± 1.57	1.31 mmHg ± 2.65	-0.05 mmHg ± 2.54
HUT PVC 3 secs	-1.19 mmHg ± 2.50	1.52 mmHg ± 2.63*	0.28 mmHg ± 1.99
HUT PVC 4 secs	-0.58 mmHg ± 1.69	1.59 mmHg ± 2.72*	0.48 mmHg ± 2.01
HUT PVC 5 secs	-0.63 mmHg ± 1.80	1.50 mmHg ± 2.68*	0.40 mmHg ± 1.97
HUT PVC 6 secs	-0.66 mmHg ± 1.92	1.37 mmHg ± 2.65*	0.41 mmHg ± 1.69

Table 2. Comparisons of postural tachycardia syndrome (PoTS) and vasovagal syncope (VVS) patients' peripheral vasoconstriction (PVC) comparative to healthy controls during pleasant image presentation on head-up tilt (HUT). ± = standard deviation, * = statistically significant (p<.05)

3.2.3 Emotionally unpleasant stimuli

There was a significant effect of interoceptive threat on ORs to unpleasant images. There were no between-group differences in OR-related ECR1 and PVC during supine unpleasant image presentation. During HUT unpleasant image presentation, there were significant between-group differences in PVC at 1 secs (F(2, 44)=5.19, p=.009), 2 secs (F(2, 44)=5.57, p=.007), 3 secs (F(2, 44)=5.39, p=.008), 4 secs (F(2, 42)=7.07, p=.002), 5 secs (F(2, 42)=6.73, p=.003) and 6 secs (F(2, 42)=7.26, p=.002). There were no significant between-group differences between PoTS and VVS patients (table 3).

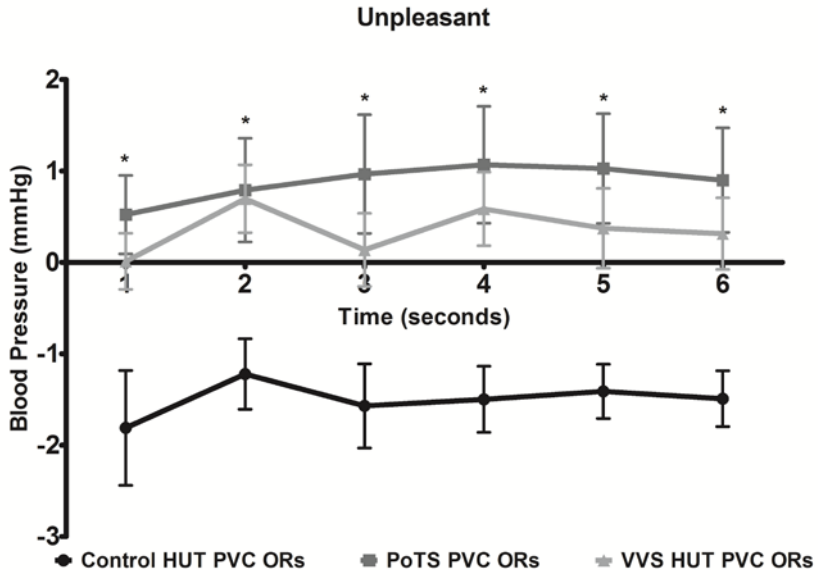

Figure 2. Stimulus intensity peripheral vasocontraction (PVC) orienting responses (ORs) to randomly presented unpleasant images during head-up tilt (HUT). PoTS = postural tachycardia syndrome, VVS = vasovagal syncope. Error bars = ± standard deviation, * = statistically significant (p<.05)

	Controls	PoTS	VVS
HUT PVC 1s	-1.81 mmHg ± 2.81	0.52 mmHg ± 1.92*	0.01 mmHg ± 1.37
HUT PVC 2s	-1.22 mmHg ± 1.72	0.79 mmHg ± 2.54*	0.70 mmHg ± 1.66*
HUT PVC 3s	-1.57 mmHg ± 2.06	0.97 mmHg ± 2.90*	0.14 mmHg ± 1.79
HUT PVC 4s	-1.50 mmHg ± 1.62	1.07 mmHg ± 2.86*	0.58 mmHg ± 1.80*
HUT PVC 5s	-1.41 mmHg ± 1.32	1.03 mmHg ± 2.68*	0.37 mmHg ± 1.95*
HUT PVC 6s	-1.49 mmHg ± 1.37	0.90 mmHg ± 2.55*	0.31 mmHg ± 1.75*

Table 3. Comparisons of postural tachycardia syndrome (PoTS) and vasovagal syncope (VVS) patients' peripheral vasoconstriction (PVC) comparative to healthy controls during unpleasant image presentation on head-up tilt (HUT). ± = standard deviation, * = statistically significant (p<.05)

4 Discussion

This study investigated psychophysiological reactivity and its potential contribution to the expression of psychological symptomatology associated with PoTS and VVS. We hypothesised that the interoceptive threat of OI symptoms would exacerbate low-order emotional reactivity (as measured by ORs) during HUT in PoTS and VVS patients in comparison to heathy controls.

Our findings indicate that cardiac and vascular responses of minimal amplitude are not only significant statistically, but also biologically in PoTS and VVS. As the OR inhibits conditioned and unconditioned reflexes, one of the aims of this experiment was to explore whether the OR was compromised by dysautonomic symptom provocation. Our data shows that, prior to patients becoming too symptomatic, the ECR1 and PVC are intact during HUT in PoTS and VVS patients. In fact, not only was the ECR1 present in PoTS patients during HUT but both PoTS and VVS patients produced greater PVC for the entirety of unpleasant image presentation during HUT compared to controls. Under the Preliminary Processing Theory, the PVC component of the OR encodes stimulus intensity, therefore, unpleasant images during HUT appeared to have greater experiential intensity for PoTS and VVS patients. There was a lower threshold for inducing orthostatic tachycardia in PoTS patients than orthostatic induction of presyncope or syncope in VVS patients. Based on our proposed model, greater autonomic arousal and accompanying symptom provocation may underpin the exaggerated and sustained PVC in PoTS patients to unpleasant image presentation on HUT in comparison to VVS patients. This may help explain the increased prevalence of psychological symptoms in PoTS patients compared to VVS (38) (50), as anxiety is amplified by somatic hypervigilance (51) and accompanied by increased attentional orienting (52) and attentional bias (53) to perceived threat. However, definitive assertion of this hypothesis requires further investigation than the current study methodology allows.

The symptomatic expression of somatic hypervigilance and attentional deficits are commonly reported by patients with PoTS and VVS (22, 23, 50). Attentional habits biased towards threat (54) and somatic hypervigilance (55) promote anxiety, these factors could be perpetuated by a having a condition that excessively increases autonomic reactivity and interoceptive threat whilst symptomatic. Moreover, the recent finding that PoTS and VVS patients' psychological symptoms are built primarily on interoception rather than trait neurosis or traumatic experience, is supported by the finding that the ECR1 (a metric of stimulus detection) was normal in both PoTS and VVS patients. Thus, the cause of the increased emotional aversion to unpleasant images was interoceptive rather than exteroceptive.

VVS patients have previously been shown to display restricted capacity for regulating their emotional states (36). Emotion regulation (ER) encapsulates a set of adaptive psychophysiological processes that support the online monitoring, evaluation and modification of emotional reactions (56) (57). PoTS patients often experience cognitive symptoms of inattention and poor short-term memory (STM), the basis of which is likely to also compromise ER through a diminished capacity to deploy attentional resources toward emotions and cognitively drive behavioural adaptations. Correspondingly, during the current study, there was a greater ER requirement for PoTS and VVS patients in terms of response modulation, impulse control and moderation of physiological response (58) when challenged by the interoceptive threat of dysautonomic symptom provocation during HUT and unpleasant image presentation. There are in two principal ER strategies; antecedent-focused and response-focused. Antecedent-focused ER regulation alters the interpretation of a stimulus (e.g. through reappraisal) to attenuate its emotional impact (57). The exaggerated emotional PVC produced by PoTS and VVS patients suggest that early-stage antecedent-focused ER strategies were either not employed or ineffective in these OI participants. Response-focused regulation occurs later in the process of emotion-generation and requires the suppression of emotional behaviours. Antecedent-focused ER strategies are ultimately more effective than suppressive response-focused strategies. This may be of relevance to the prevalence of psychopathology in OI since, while reappraisal dampens emotional experience and subsequent behavioural expression, it may not impact initial perceptual encoding to the same degree. Response-focused suppression decreases behavioural markers of emotion but often paradoxically increases internal physiological responses (e.g. exaggerated OR-related PVC). Impaired memory (59) and associated cognitive symptom in PoTS (57), may have their origin in this mismatch between automatic physiological and volitional responses to salient stimuli. Based on the current findings, VVS and PoTS patients in particular appear biased toward response-focused ER strategies when

symptomatic, since autonomic pathology and excessive arousal negates antecedent-focused ER. The current findings might both explain previous observations of reduced anticipation and regulation of emotional states in VVS (36) and suggest these deficits are common in other forms of OI, such as PoTS.

ER difficulties, particularly those that disrupt physiological emotional responses, are implicated in a number of psychopathological states and anxiety disorders (60). ER's modulation of spontaneous emotional responses is reflected in concomitant autonomic reactivity (61) (62) (63) (64, 65). However, during symptom provocation, PoTS and VVS patients are unable to fully regulate their autonomic responses to emotive stimuli. Our findings suggest this predisposes to impaired ER and - by extension - to somatic anxiety (38). The active compensation for the initial perturbation of emotional and interoceptive processing, perhaps constraining the availability of cognitive resources for other processes, thus contributes to cognitive symptoms, as supported by our recent application of a predictive coding framework to integrated interoceptive and autonomic function and dysfunction in PoTS and VVS (6) (66).

Our study support our previous findings that dysautonomia has a causative role in the subclinical but significant (both objectively and subjectively) cognitive and emotional symptoms that PoTS and VVS patients experience (38). As the current study demonstrates, interoceptive signals of autonomic dysfunction ascend the cortical hierarchy into conscious perception when patients are symptomatic, thereby disrupting ongoing psychological processes. Our observations provide further support for an association between dysautonomia and emotional dysregulation. Our findings also make predictions about the underlying neural mechanism that can be validated using neuroimaging. Our focus on objective psychophysiological measures contrasts with other studies focusing on detailed subjective measures of emotional intensity. However, it is a limitation that we did not capitalize on both approaches. Moreover, neither antecedent nor response-focused ER strategies were directly measured, representing a limitation to interpretation. In our female participants, we did explicitly control for timing of menses, which is known to exacerbate autonomic symptoms in PoTS patients probably because of hormonal fluctuations within the cycle. This should be considered for any subsequent studies. We recognise the value of extending the number of participants in future research to explore whether increased power will reveal effects of pleasant or neutral emotional stimuli. This might deepen our understanding of ER in disorders of autonomic overexcitation. The inclusion of defined paradigms to measure ER strategies at rest and during symptom provocation would allow us to test our prediction

that there are differences in ER strategies between PoTS, VVS patients and controls. Refining knowledge concerning how ER strategy-selection predisposes OI patients groups to experience emotional and cognitive symptoms.

Conclusions

This study investigated psychophysiological contributions to emotional symptomatology in common forms of OI. PoTS and VVS patients produced greater indices of emotional responsivity to unpleasant images and, to a lesser degree, pleasant images, during HUT when the interoceptive threat of autonomic dysfunction was provoked. This cross-valance (both unpleasant and pleasant images) finding indicates abnormal ER processes. We argue that this provides a mechanistic underpinning of how pathological autonomic overexcitation predisposes to anxiogenic traits in PoTS and VVS patients. Our model also accounts for normal correlates of stimulus detection in both OI patient groups, consistent with the increased aversion to unpleasant stimuli being interocepitvely rather than exteroceptively derived. We provide further empirical support that interoception of (dys)autonomic function drives subclinical psychopathology in PoTS and VVS. Relatedly, these patients may be predisposed to response-focused ER whilst symptomatic, as exaggerated autonomic responsivity negates antecedent-focused ER. This hypothesis may improve our understanding of why orthostasis exacerbates cognitive symptoms in these patients despite normative cerebral autoregulation. The top-down silencing of aberrant interoceptive feedback (and its hierarchical representation in interoceptive prediction errors) during OI evokes a greater top-down suppression of interoceptive signalling and may compromise other cognitive processes. Together, our findings elucidate novel aspects of the psychophysiology of OI and provides a therapeutic target for behavioural therapies aimed at reducing psychopathology in PoTS and VVS patients.

Competing interests:

Dr Andrew Owens reports no disclosures
Dr David Low reports no disclosures
Prof Christopher Mathias reports no disclosures
Prof Hugo Critchley reports no disclosures

Acknowledgments:
We would like to thank all those who participated in and supported this study. APO was funded by a research fellowship from the Autonomic Charitable Trust and the St Mary's Development Trust.

References

1. Damasio AR. The feeling of What Happens: Body and Emotion in the Making of Consciousness. New York: Harcourt Brace; 1999.
2. Gray MA, Beacher FD, Minati L, Nagai Y, Kemp AH, Harrison NA, et al. Emotional appraisal is influenced by cardiac afferent information. Emotion. 2012;12:180-91.
3. Lange CG, James W. The Emotions Baltimore: Williams & Wilkins Company; 1922.
4. Garfinkel SN, Tiley C, O'Keeffe S, Harrison NA, Seth AK, Critchley HD. Discrepancies between dimensions of interoception in autism: Implications for emotion and anxiety. Biological psychology. 2016;114:117-26.
5. Paulus MP, Stein MB. An insular view of anxiety. Biological psychiatry. 2006;60(4):383-7.
6. Owens A.P., Allen M., Ondobaka S, Friston K.J. Interoceptive inference: from computational neuroscience to clinic. Neuroscience & Biobehavioral Reviews. Under review.
7. Skinner JE. Regulation of cardiac vulnerability by the frontal cortex: a new concept of Cannon's cerebral defense mechanism. In: Gailbraith GC, Kietzman, M.L., Donchin, E., editor. Neurophysiology and Psychophysiology: Experimental and Clinical Applications. Hillsdale, NJ.: Lawrence Erlbaum; 1988. p. 68-80.
8. Schondorf R, Benoit J, Wein T, Phaneuf D. Orthostatic intolerance in the chronic fatigue syndrome. Journal of the autonomic nervous system. 1999;75(2-3):192-201.
9. Vaddadi G, Lambert E, Corcoran SJ, Esler MD. Postural syncope: mechanisms and management. The Medical journal of Australia. 2007;187(5):299-304.
10. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Autonomic neuroscience : basic & clinical. 2011;161(1-2):46-8.
11. Mathias CJ, Low DA, Iodice V, Owens AP, Kirbis M, Grahame R. Postural tachycardia syndrome--current experience and concepts. Nature reviews Neurology. 2012;8(1):22-34.
12. Thieben MJ, Sandroni P, Sletten DM, Benrud-Larson LM, Fealey RD, Vernino S, et al. Postural orthostatic tachycardia syndrome: the Mayo clinic experience. Mayo Clinic proceedings. 2007;82(3):308-13.
13. Schondorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? Neurology. 1993;43(1):132-7.
14. Parsaik A, Allison TG, Singer W, Sletten DM, Joyner MJ, Benarroch EE, et al. Deconditioning in patients with orthostatic intolerance. Neurology. 2012;79(14):1435-9.
15. Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. Mayo Clinic proceedings. 2012;87(12):1214-25.
16. Medow MS, Stewart JM, Sanyal S, Mumtaz A, Sica D, Frishman WH. Pathophysiology, diagnosis, and treatment of orthostatic hypotension and vasovagal syncope. Cardiology in review. 2008;16(1):4-20.
17. Barcroft H, Edholm OG. On the vasodilatation in human skeletal muscle during post-haemorrhagic fainting. The Journal of physiology. 1945;104(2):161-75.
18. Sledge WH. Antecedent psychological factors in the onset of vasovagal syncope. Psychosomatic medicine. 1978;40(7):568-79.
19. Owens AP., Low DA., Iodice V., Mathias CJ., HD C. Emotion and the autonomic nervous system – a 'two-way street': Insights from autonomic, affective and dissociative disorders. In: Rolls E, editor. Reference Module in Neuroscience and Biobehavioral Psychology: Elsevier SciTech Connect; In press.
20. Critchley HD EJ, Garfinkel SN. Interaction between cognition, emotion, and the autonomic nervous system. Handb Clin Neurol 2013(117:):59-77.
21. Eccles JA, Owens AP, Mathias CJ, Umeda S, Critchley HD. Neurovisceral phenotypes in the expression of psychiatric symptoms. Frontiers in neuroscience. 2015;9:4.
22. Benrud-Larson LM, Sandroni P, Haythornthwaite JA, Rummans TA, Low PA. Correlates of functional disability in patients with postural tachycardia syndrome: preliminary cross-sectional findings. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 2003;22(6):643-8.

23. Raj V, Haman KL, Raj SR, Byrne D, Blakely RD, Biaggioni I, et al. Psychiatric profile and attention deficits in postural tachycardia syndrome. Journal of neurology, neurosurgery, and psychiatry. 2009;80(3):339-44.
24. Masuki S, Eisenach JH, Johnson CP, Dietz NM, Benrud-Larson LM, Schrage WG, et al. Excessive heart rate response to orthostatic stress in postural tachycardia syndrome is not caused by anxiety. J Appl Physiol. 2007;102(3):896-903.
25. Raj SR. The Postural Tachycardia Syndrome (POTS): pathophysiology, diagnosis & management. Indian Pacing Electrophysiol J. 2006;6(2):84-99.
26. Bagai K, Song Y, Ling JF, Malow B, Black BK, Biaggioni I, et al. Sleep disturbances and diminished quality of life in postural tachycardia syndrome. J Clin Sleep Med. 2011;7(2):204-10.
27. Anderson JW, Lambert EA, Sari CI, Dawood T, Esler MD, Vaddadi G, et al. Cognitive function, health-related quality of life, and symptoms of depression and anxiety sensitivity are impaired in patients with the postural orthostatic tachycardia syndrome (POTS). Frontiers in physiology. 2014;5:230.
28. Ocon AJ. Caught in the thickness of brain fog: exploring the cognitive symptoms of Chronic Fatigue Syndrome. Frontiers in physiology. 2013;4:63.
29. Ross AJ, Medow MS, Rowe PC, Stewart JM. What is brain fog? An evaluation of the symptom in postural tachycardia syndrome. Clinical autonomic research : official journal of the Clinical Autonomic Research Society. 2013;23(6):305-11.
30. Graham DT. Prediction of fainting in blood donors. Circulation. 1961;23:901-6.
31. McGrady A, Kern-Buell C, Bush E, Khuder S, Grubb BP. Psychological and physiological factors associated with tilt table testing for neurally mediated syncopal syndromes. Pacing and clinical electrophysiology : PACE. 2001;24(3):296-301.
32. Luborsky L, Docherty JP, Penick S. Onset conditions for psychosomatic symptoms: a comparative review of immediate observation with retrospective research. Psychosomatic medicine. 1973;35(3):187-204.
33. Karaca S, Emul M, Kulac M, Yuksel S, Ozbulut O, Guler O, et al. Temperament and character profile in patients with essential hyperhidrosis. Dermatology. 2007;214(3):240-5.
34. Cohen TJ, Thayapran N, Ibrahim B, Quan C, Quan W, von zur Muhlen F. An association between anxiety and neurocardiogenic syncope during head-up tilt table testing. Pacing and clinical electrophysiology : PACE. 2000;23(5):837-41.
35. Lerma A, Lerma C, Marquez MF, Cardenas M, Hermosillo AG. Correlation of syncopal burden with anxiety symptoms score in recurrent vasovagal syncope. International journal of cardiology. 2013;166(1):266-7.
36. Buodo G, Sarlo M, Poli S, Giada F, Madalosso M, Rossi C, et al. Emotional anticipation rather than processing is altered in patients with vasovagal syncope. Clin Neurophysiol. 2012;123(7):1319-27.
37. Lkhagvasuren B, Masuno T, Kanemitsu Y, Sudo N, Kubo C, Oka T. Increased prevalence of postural orthostatic tachycardia syndrome in psychogenic fever patients. Psychotherapy and psychosomatics. 2013;82(4):269-70.
38. Owens AP, Low DA, Iodice V, Critchley HD, Mathias CJ. The genesis and presentation of anxiety in disorders of autonomic overexcitation. Autonomic neuroscience : basic & clinical. 2017;203:81-7.
39. Fanselow MS. Neural organization of the defensive behavior system responsible for fear. Psychonomic bulletin & review. 1994;1(4):429-38.
40. Hermans EJ, Henckens MJ, Roelofs K, Fernandez G. Fear bradycardia and activation of the human periaqueductal grey. NeuroImage. 2013;66:278-87.
41. Pavlov IP. [Application of the results of our animal experiments to man]. Das Deutsche Gesundheitswesen. 1953;8(2):32-40.
42. Sokolov EN. Higher nervous functions; the orienting reflex. Annual review of physiology. 1963;25:545-80.
43. Barry RJ. Habituation of the orienting reflex and the development of Preliminary Process Theory. Neurobiology of learning and memory. 2009;92(2):235-42.
44. Barry RJ. The effect of “significance” upon indices of Sokolov's orienting response: A new conceptualisation to replace the OR. . Physiological Psychology. 1977(5):209–14.

45. Buchanan TW, Etzel JA, Adolphs R, Tranel D. The influence of autonomic arousal and semantic relatedness on memory for emotional words. International journal of psychophysiology : official journal of the International Organization of Psychophysiology. 2006;61(1):26-33.
46. Fernandez MC, Vila J. Sympathetic-parasympathetic mediation of the cardiac defense response in humans. Biological psychology. 1989;28(2):123-33.
47. Graham FK. Constraints on measuring heart rate and period sequentially through real and cardiac time. Psychophysiology. 1978;15(5):492-5.
48. Lang PJ BM, Cuthbert BN. International Affective Picture System (IAPS): Affective ratings of pictures and instruction manual. 2005.
49. Jasson S, Medigue C, Maison-Blanche P, Montano N, Meyer L, Vermeiren C, et al. Instant power spectrum analysis of heart rate variability during orthostatic tilt using a time-/frequency-domain method. Circulation. 1997;96(10):3521-6.
50. Owens AP, Low DA, Critchley HD, Mathias CJ. Intermittent Autonomic Disorders and Emotion: A Two-way Street? Autonomic Neuroscience: Basic and Clinical; Stresa, Italy2015. p. 136.
51. Wilhelm FH, Roth WT. The somatic symptom paradox in DSM-IV anxiety disorders: suggestions for a clinical focus in psychophysiology. Biological psychology. 2001;57(1-3):105-40.
52. Bar-Haim Y, Lamy D, Pergamin L, Bakermans-Kranenburg MJ, van IMH. Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. Psychological bulletin. 2007;133(1):1-24.
53. Eysenck MW, Derakshan N, Santos R, Calvo MG. Anxiety and cognitive performance: attentional control theory. Emotion. 2007;7(2):336-53.
54. Mathews A. Why worry? The cognitive function of anxiety. Behaviour research and therapy. 1990;28(6):455-68.
55. Verkuil B, Brosschot JF, Thayer JF. A sensitive body or a sensitive mind? Associations among somatic sensitization, cognitive sensitization, health worry, and subjective health complaints. Journal of psychosomatic research. 2007;63(6):673-81.
56. Stifter CA, Dollar JM, Cipriano EA. Temperament and emotion regulation: the role of autonomic nervous system reactivity. Developmental psychobiology. 2011;53(3):266-79.
57. Gross JJ. Emotion regulation: affective, cognitive, and social consequences. Psychophysiology. 2002;39(3):281-91.
58. Hoeksma JB, Oosterlaan J, Schipper EM. Emotion regulation and the dynamics of feelings: a conceptual and methodological framework. Child development. 2004;75(2):354-60.
59. Garfinkel SN, Barrett AB, Minati L, Dolan RJ, Seth AK, Critchley HD. What the heart forgets: Cardiac timing influences memory for words and is modulated by metacognition and interoceptive sensitivity. Psychophysiology. 2013;50(6):505-12.
60. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. Biological psychiatry. 1996;39(4):255-66.
61. Koole SL, Rothermund K. "I feel better but I don't know why": the psychology of implicit emotion regulation. Cognition & emotion. 2011;25(3):389-99.
62. Denson TF, Creswell JD, Terides MD, Blundell K. Cognitive reappraisal increases neuroendocrine reactivity to acute social stress and physical pain. Psychoneuroendocrinology. 2014;49:69-78.
63. Kennedy DO, Scholey AB. Glucose administration, heart rate and cognitive performance: effects of increasing mental effort. Psychopharmacology. 2000;149(1):63-71.
64. Blair C. Behavioral inhibition and behavioral activation in young children: relations with self-regulation and adaptation to preschool in children attending Head Start. Developmental psychobiology. 2003;42(3):301-11.
65. Stifter CA, Jain A. Psychophysiological correlates of infant temperament: stability of behavior and autonomic patterning from 5 to 18 months. Developmental psychobiology. 1996;29(4):379-91.
66. Owens AP, Friston KJ, Low DA, Mathias CJ, Critchley HD. Investigating the relationship between cardiac interoception and heart rate variability via a predictive coding framework. Autonomic Neuroscience: Basic and Clinical. Under review.